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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/717,735	11/19/2003	Christopher R. Wagstrom	37210-8004.US00	8693

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EXAMINER	
STEELE, AMBER D	
ART UNIT	**PAPER NUMBER**
1639	

DATE MAILED: 08/01/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/717,735	WAGSTROM ET AL.	
	Examiner	Art Unit	
	Amber D. Steele	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 May 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-38* is/are pending in the application.

4a) Of the above claim(s) *5,7-10,12,14,22-24,27,28,32-34 and 36-38* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4, 6, 11, 13, 16-21, 25-26, 30-31, 35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Status of the Claims

2. Claims 41-81 were cancelled by Applicants in the preliminary amendment received on November 11, 2003.

Claims 39-40 were cancelled by Applicants in the amendment received on August 29, 2005.

Claims 1-38 are currently pending.

Claims 1-4, 6, 11, 13, 16-21, 25-26, 30-31, and 35 are currently under consideration.

Please note that claims 7 and 15 are designated as original in the amendment to the claims received on May 3, 2006, however the claims were withdrawn in the Office action mailed on November 3, 2005. Appropriate correction is required. Please refer to MPEP § 714 and 37 CFR 1.121.

Election/Restriction

3. Regarding applicants' assertion that claims 7 and 15 read on the elected species, the following remarks are made:

Claim 7 is drawn to a Fv antibody fragment wherein the art recognized definition of Fv fragments are that only the variable domains of the antibody are present. Therefore, the amendment to the claim received on May 3, 2006 stating that "the first and third polypeptide

segments comprise the variable domains and constant domain of the light and heavy chains, respectively, of a single antibody such that when the first and third segments associate, the product is an Fv antibody fragment" is contradictory to the art recognized definition of an Fv. An antibody fragment comprising the constant domains would be defined as Fab. In addition, applicants elected antibody variable and constant regions as the species of first and third polypeptide segment which Fv does not read on. Please refer to paragraphs 11-12 of the present specification.

Claim 15 is drawn to a peptide sequence of SEQ ID NO: 1 (Asp Pro). Applicants elected a disordered region cleavable by urokinase as the species of cleavable peptide sequence. Urokinase is known in the art to cleave the bond between Arg-Val (e.g. not Asp Pro). Furthermore, the specification does not provide guidance that SEQ ID NO: 1 is cleavable by urokinase. Moreover, the specification specifically teaches that Asp-Pro (e.g. SEQ ID NO: 1) is an autocleaving sequence, which cleaves under acidic conditions. Please refer to paragraphs 16, 44, 117, and 122 of the present specification.

Therefore, claims 7 and 15 do not read on the elected species and are withdrawn from further consideration.

Drawings

4. The drawings were received on May 3, 2006. These drawings are entered and considered.

Withdrawn Objections or Rejections

5. The amendments to the drawings and the specification received on May 3, 2006 overcome the objection to the drawings made in the Office action mailed on November 3, 2005.

6. The amendment to the specification received on May 3, 2006 overcome the objection to the specification made in the Office action mailed on November 3, 2006.

7. Upon further consideration, the objection to claim 16 under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim is withdrawn.

Maintained Rejections

Claim Rejection - 35 USC § 102

8. Claims 1-4, 6, 11, 13, 16-21, 25-26, 30-31, and 35 are rejected under 35 U.S.C. 102(b) as being anticipated by Ladner *et al.* U.S. Patent No. 5,223,409 issued June 29, 1993.

Ladner *et al.* teach binding proteins displayed on the outer surfaces of filamentous phage or cells (please refer to column 1, lines 40-52). Ladner *et al.* teach that the display system may be utilized to develop antibodies (please refer to column 15, lines 65-68) as further evidenced by Ladner *et al.* (U.S. Patent No. 4,949,778 issued August 7, 1990; column 8, lines 62-67, column 15, lines 45-52, column 33, lines 56-68, and column 34, lines 1-57). In addition, Ladner *et al.* teach V_L-linker-V_H as single-chain antigen-binding fragment and V_L-C_L bound to V_H-C_{H1} as fragment antibodies (e.g. present claims 1-4 and 6; please refer to column 15, lines 34-64).

Furthermore, Ladner *et al.* teach the display system as a binding domain operably linked to a signal sequence (e.g. OmpA and present claim 17; please refer to column 61, lines 39-53, column 62, lines 31-33, and column 63, lines 28-48) and a coat protein (e.g. M13 gene III and present claims 18 and 25; please refer to column 51, line 51 and column 54, lines 48-50) so that the expression product is transported to the inner membrane of the host cell (e.g. *E. coli* and present claims 25 and 35; please refer to column 56, lines 6-14 and column 61, lines 21-23) and trapped until the single-stranded DNA of the nascent phage particle collects both the wild type coat protein and the hybrid protein from the lipid bilayer and packages the hybrid protein into the surface sheath of the filamentous phage (e.g. M13 and present claims 19-21 and 25-26; please refer to column 54, lines 37-38 and column 55, lines 36-60) thereby exposing the hybrid protein on the replicable genetic package (please refer to column 51, lines 33-68 and column 52, lines 1-11). Lander *et al.* also teach the use of flexible linkers that encode a recognition site for a specific protease including Factor Xa (e.g. present claims 11, 13, 16 and 30-31, please refer to column 57, lines 39-59, column 58, lines 1-18, column 70, lines 64-68, column 71, lines 1-5, and column 73, lines 20-40). Therefore, one of ordinary skill in the art would have anticipated the present invention of claims 1-4, 6, 11, 13, 16-21, 25-26, 30-31, and 35 in view of the teachings of Ladner *et al.*

Arguments and Response

9. Applicants' argument directed to the rejection under 35 USC 102(b) as being anticipated by Ladner *et al.* U.S. Patent No. 5,223,409 issued June 29, 1993 for claims 1-4, 6, 11, 13, 16-21, 25-26, 30-31, and 35 was considered but are not persuasive for the following reasons.

Applicants allege that Ladner et al. does not teach a second polypeptide segment having therein a cleavable peptide sequence cleavable by a proteolytic agent. In addition, Applicants allege that Ladner et al. teach DNA molecules encoding chimeric protein comprising a display sequence and a binding domain where the display sequence directs secretion of the binding domain. Furthermore, the applicants suggest that the Examiner relied on the cleavable signal sequence at the terminal end of the protein as the cleavable sequence.

Applicants' arguments are not convincing since the teachings of Ladner et al. anticipate the expression vector of the instant claims. It is the Examiner's position that Ladner et al. teach VL-linker-VH sequences with or without antibody conserved regions wherein VL is the first polypeptide segment, the linker is the second polypeptide segment, and VH is the third polypeptide segment (please refer to column 15). In addition, Ladner et al. teach that PBD/IPBD-linker-OSP wherein the PBD is the potential binding domain/first polypeptide, linker is the second polypeptide, and OSP is the outer surface protein/third polypeptide (please refer to columns 18, 55-58, 70-71). Additionally, Ladner et al. teach that the linkers can be cleavable via proteolytic agents (please refer to columns 57-58 and 70-71). Furthermore, the signal sequence is not relied upon as the cleavable sequence, but as part of the evidence that the expression vector can be expressed on the surface of a genetically replicable package and as the third polypeptide. Therefore, Ladner et al. teaches a second sequence that can be cleaved.

Claim Rejection - 35 USC § 102

10. Claims 1-4, 6, 11, 13, 16-21, 25-26, 30, and 35 are rejected under 35 U.S.C. 102(b) as being anticipated by Griffiths *et al.* U.S. Patent No. 5,962,255 issued October 5, 1999.

Griffiths *et al.* teach methods and recombinant host cells for the production of antibodies displayed on the surface of replicable genetic display packages or rgdps (e.g. filamentous phage) via vectors comprising nucleic acids encoding a first and second polypeptide for a specific binding pair or sbp (please refer to the "Abstract"). Griffiths *et al.* also teach the first polypeptide as the variable and constant regions of an antibody light chain (e.g. V_L and C_L), the second polypeptide as the variable and constant regions of an antibody heavy chain (e.g. V_H and C_H or V_H and C_{H1}) with a g3 anchoring peptide (e.g. pIII, gIII, or coat protein III; present claims 18 and 25), and an intervening sequence encoding a selectable "marker peptide" and a loxP site (e.g. a first polypeptide encoding V_L/C_L, a second polypeptide with a cleavable sequence, and a third polypeptide encoding V_H/C_H having an anchor peptide of present claims 1-4, 6, 16, 18, 25, and 30; please refer to Figures 3-4, 6-7, 14-19 and columns 19-21, 24, and 28). Griffiths *et al.* also teach the Cre recombinase which cleaves the loxP site of the intervening sequence and is expressed in a separate plasmid (e.g. enzymatic proteolytic agent of present claims 11, 13, and 30; please refer to column 52, lines 45-55 and column 53, lines 19-24). In addition, Griffiths *et al.* teach that the replicable genetic display package can be a M13 bacteriophage or *E. coli* infected with an M13 bacteriophage (e.g. present claims 19-21, 25-26, and 35; please refer to column 7, lines 52-60, column 22, lines 59-67, and column 24, lines 3-35). Furthermore, Griffiths *et al.* teaches that a secretory leader peptide such as OmpA can be utilized to display the polypeptides (e.g. present claim 17; please refer to column 22, lines 65-66). Therefore, one of skill in the art would have anticipated the present invention of claims 1-4, 6, 11, 13, 16-21, 25-26, 30, and 35 in view of the teachings of Griffiths *et al.*

Arguments and Response

11. Applicants' argument directed to the rejection under 35 USC 102(b) as being anticipated by Griffiths *et al.* U.S. Patent No. 5,962,255 issued October 5, 1999 for claims 1-4, 6, 11, 13, 16-21, 25-26, 30, and 35 was considered but are not persuasive for the following reasons.

Applicants allege that Griffiths et al. does not teach a second polypeptide segment having therein a cleavable peptide sequence cleavable by a proteolytic agent.

Applicants' arguments are not convincing since the teachings of Griffiths et al. anticipate the expression vector of the instant claims. It is the Examiner's position that Griffiths *et al.* teach the first polypeptide as V_L and C_L, the second polypeptide as the selectable "marker peptide" and a loxP site, and the third polypeptide as V_H and C_H or V_H and C_{H1} with a g3 anchoring peptide (e.g. pIII, gIII, or coat protein III; present claims 18 and 25) (please refer to Figures 3-4, 6-7, 14-19 and columns 19-21, 24, and 28). Griffiths *et al.* also teach the Cre recombinase, which cleaves the loxP site of the intervening sequence (e.g. second sequence) and is expressed in a separate plasmid (please refer to column 52, lines 45-55 and column 53, lines 19-24). Therefore, Griffiths et al. teach a second sequence that can be cleaved.

Claim Rejection - 35 USC § 102

12. Claims 1-4, 6, 11, 13, 16-21, 25-26, 30-31, and 35 are rejected under 35 U.S.C. 102(e) as being anticipated by Wang *et al.* U.S. Paten No. 6,833,441 B2 filed August 1, 2001.

Wang *et al.* teach recombinant polynucleotides, vectors, and host cells for producing antigen-binding units (e.g. present claim 35; please refer to the "Abstract"). Wang *et al.* teach a light chain variable region fused to a heterodimerization sequence (e.g. first polypeptide), a

"flexon" (e.g. second polypeptide), a heavy chain variable region fused to a second hetrodimerization sequence (e.g. third polypeptide) in a phage display vector and a host cell (e.g. present claims 1-3; please refer to column 4, lines 21-30, column 5, lines 48-61, column 6, lines 45-63,column 20, lines 1-15, column 26, lines 54-64, and column 38, lines 1-39). Additionally, Wang *et al.* also teach V_L, V_H, C_L, C_H, and C_{H1} (e.g. present claims 4 and 6; please refer to column 12, lines 3-10). In addition, Wang *et al.* teach the phage display vector as the filamentous phage M13 and fusion of antibody peptides to a phage coat protein specifically pIII of M13 (e.g. present claims 18-21 and 25-26; please refer to column 13, lines 47-52 and column 29, lines 49-65). Furthermore, Wang *et al.* also teach the use of OmpA for display in bacterial host cells including *E. coli* (e.g. present claim 17 and 25; please refer to column 30, lines 39-49 and column 35, lines 16-22). Moreover, Wang *et al.* teach protease cleavage sites between the heterodimerization sequences and phage coat protein (e.g. present claims 11, 13, 16, and 30-31; please refer to column 37, lines 1-7). Therefore, one of skill in the art would have anticipated the present invention of claims 1-4, 6, 11, 13, 16-21, 25-26, 30-31, and 35 in view of the teachings by Wang *et al.*

Arguments and Response

13. Applicants' argument directed to the rejection under 35 USC 102(e) as being anticipated by Wang *et al.* U.S. Paten No. 6,833,441 B2 filed August 1, 2001 for claims 1-4, 6, 11, 13, 16-21, 25-26, 30-31, and 35 was considered but are not persuasive for the following reasons.

Applicants allege that Wang et al. does not teach a second polypeptide segment having therein a cleavable peptide sequence cleavable by a proteolytic agent. In addition, Applicants

allege that Wang et al. teach two proteins rather than a single polypeptide sequence having three polypeptide segments.

Applicants' arguments are not convincing since the teachings of Wang et al. anticipate the expression vector of the instant claims. It is the Examiner's position that Wang *et al.* teach a light chain variable region fused to a heterodimerization sequence (e.g. first polypeptide), a "flexon" (e.g. second polypeptide), a heavy chain variable region fused to a second hetrodimerization sequence (e.g. third polypeptide) in a phage display vector and a host cell (e.g. please refer to column 4, lines 21-30, column 5, lines 48-61, column 6, lines 45-63,column 20, lines 1-15, column 26, lines 54-64, and column 38, lines 1-39). In addition, Wang *et al.* teach protease cleavage sites (e.g. second polypeptide) between the heterodimerization sequences (e.g. first polypeptide) and phage coat protein (e.g. third polypeptide; please refer to column 37, lines 1-7). In addition, the invention as claimed does not state that the three polypeptide sequences must be derived from a single polypeptide. Therefore, Wang et al. teach a second sequence that can be cleaved.

Claim Rejections - 35 USC § 103

14. Claims 1-4, 6, 11, 13, 16-21, 25-26, 30-31, and 35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ladner *et al.* U.S. Patent No. 5,223,409 issued June 29, 1993 and Goers *et al.* U.S. Patent No. 4,867,973 issued September 19, 1989.

Ladner *et al.* teach binding proteins displayed on the outer surfaces of filamentous phage or cells (please refer to column 1, lines 40-52). Ladner *et al.* teach that the display system may be utilized to develop antibodies (please refer to column 15, lines 65-68) as further evidenced by

Ladner *et al.* (U.S. Patent No. 4,949,778 issued August 7, 1990; column 8, lines 62-67, column 15, lines 45-52, column 33, lines 56-68, and column 34, lines 1-57). In addition, Ladner *et al.* teach V_L-linker-V_H as single-chain antigen-binding fragment and V_L-C_L bound to V_H-C_{H1} as fragment antibodies (e.g. present claims 1-4 and 6; please refer to column 15, lines 34-64). Furthermore, Ladner *et al.* teach the display system as a binding domain operably linked to a signal sequence (e.g. OmpA and present claim 17; please refer to column 61, lines 39-53, column 62, lines 31-33, and column 63, lines 28-48) and a coat protein (e.g. M13 gene III and present claims 18 and 25; please refer to column 51, line 51 and column 54, lines 48-50) so that the expression product is transported to the inner membrane of the host cell (e.g. *E. coli* and present claims 25 and 35; please refer to column 56, lines 6-14 and column 61, lines 21-23) and trapped until the single-stranded DNA of the nascent phage particle collects both the wild type coat protein and the hybrid protein from the lipid bilayer and packages the hybrid protein into the surface sheath of the filamentous phage (e.g. M13 and present claims 19-21 and 25-26; please refer to column 54, lines 37-38 and column 55, lines 36-60) thereby exposing the hybrid protein on the replicable genetic package (please refer to column 51, lines 33-68 and column 52, lines 1-11). Lander *et al.* also teach the use of flexible linkers that encode a recognition site for a specific protease including Factor Xa (e.g. present claims 11, 13, 16 and 30-31, please refer to column 57, lines 39-59, column 58, lines 1-18, column 70, lines 64-68, column 71, lines 1-5, and column 73, lines 20-40).

However, Lander *et al.* do not teach a disordered region cleavable by urokinase.

Goers et al. *et al.* teach attachment of a therapeutic agent to antibodies via a linker which may be cleavable by urokinase (e.g. please refer to column 3, lines 14-31). Goers *et al.* further

teach that the linker can be an amine, a branched linker, proteolytic peptide linkers cleavable by urokinase, or a linker may have a spacer and a cleavable portion of a random construction (e.g. present claim 11, 29-31; please refer to columns 21-22, Tables III-V and VII-VIII, Example: Series IV-V). Therefore, Goers *et al.* specifically teaches a urokinase cleavable linker.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the antigen-binding polypeptide display system of Ladner *et al.* and incorporate the urokinase peptide cleavage sequences of Goers *et al.*

One having ordinary skill in the art would have been motivated to do this because Goers *et al.* teaches that the linkage of the therapeutic agent to the antibody may interfere with antigen binding and potentially reduce the effectiveness of the therapeutic system, therefore, the use of a cleavage site to release the therapeutic agent from the antibody would be beneficial (please refer to column 4, lines 7-27 of Goers *et al.*). Furthermore, Lander *et al.* teach the use of flexible linkers that encode a recognition site for a specific protease including Factor Xa (e.g. present claims 16 and 30-31, please refer to column 57, lines 39-59, column 58, lines 1-18, column 70, lines 64-68, column 71, lines 1-5, and column 73, lines 20-40). Therefore, a urokinase cleavable peptide linker taught by Goers *et al.* could be utilized to increase antigen binding by the proteins displayed by genetically replicable packages taught by Ladner *et al.*

There is a reasonable expectation of success in the modification of the antibody display system taught by Ladner *et al.* with the urokinase cleavage sequence of Goers *et al.* because of the examples in Goers *et al.* showing the success of urokinase cleavable linkers joining antibodies to therapeutic agents or cells (please refer to sections 9.1-9.4 and 10.2-10.4 in Goers *et al.*).

Therefore, the modification of the antibody display system by Lander *et al.* with the urokinase cleavable sequence by Goers *et al.* would render the instant claims prima facie obvious.

Arguments and Response

15. Applicants' argument directed to the rejection under 35 USC 103(a) as being unpatentable over Ladner *et al.* U.S. Patent No. 5,223,409 issued June 29, 1993 and Goers *et al.* U.S. Patent No. 4,867,973 issued September 19, 1989 for claims 1-4, 6, 11, 13, 16-21, 25-26, 30-31, and 35 was considered but was not found persuasive for the following reasons.

Applicants allege that Ladner et al. are not particularly concerned with the difficulties of developing anchored antibodies and that Goers et al. is cited merely for the teaching of a urokinase peptide cleavage sequence.

Applicants' arguments are not convincing since the combined teachings of Ladner et al. and Goers et al. render the expression vector of the instant claims *prima facie* obvious. It is the Examiner's position that indeed Ladner et al. does state that the preferred embodiment for the binding domain is not antibody however the presently claimed invention is not limited to antibodies and Ladner et al. still teaches that the expression vectors can be utilized for antibodies (please refer to columns 15-16). In aadition, Ladner et al. teach VL-linker-VH sequences with or without antibody conserved regions wherein VL is the first polypeptide segment, the linker is the second polypeptide segment, and VH is the third polypeptide segment (please refer to column 15). Furthermore, Ladner et al. teach that PBD/IPBD-linker-OSP wherein the PBD is the potential binding domain/first polypeptide, linker is the second polypeptide, and OSP is the outer surface protein/third polypeptide (please refer to columns 18, 55-58, 70-71). Additionally,

Ladner et al. teach that the linkers can be cleavable via proteolytic agents (please refer to columns 57-58 and 70-71). Moreover, the signal sequence is not relied upon as the cleavable sequence, but as part of the evidence that the expression vector can be expressed on the surface of a genetically replicable package and as the third polypeptide. Goers et al. is in fact utilized as evidence for a urokinase peptide cleavage sequence that can be attached to antibodies in order to ensure proper antigen binding (please refer to columns 3-4 and 21-22). In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Therefore, the teachings of Ladner et al. and Goers et al. render the instant claims *prima facie* obvious.

Claim Rejections - 35 USC § 103

16. Claims 1-4, 6, 11, 13, 16-21, 25-26, 29-31, and 35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Griffiths *et al.* U.S. Patent No. 5,962,255 issued October 5, 1999 and Goers *et al.* U.S. Patent No. 4,867,973 issued September 19, 1989.

Griffiths *et al.* teach methods and recombinant host cells for the production of antibodies displayed on the surface of replicable genetic display packages or rgdps (e.g. filamentous phage) via vectors comprising nucleic acids encoding a first and second polypeptide for a specific binding pair or sbp (please refer to the "Abstract"). Griffiths *et al.* also teach the first polypeptide as the variable and constant regions of an antibody light chain (e.g. V_L and C_L), the second polypeptide as the variable and constant regions of an antibody heavy chain (e.g. V_H and C_H or

V_H and C_{H1}) with a g3 anchoring peptide (e.g. pIII, gIII, or coat protein III; present claims 18 and 25) at the N-terminus, with an intervening sequence encoding a selectable "marker peptide" and a loxP site (e.g. a first polypeptide encoding V_L/C_L, a second polypeptide with a cleavable sequence, and a third polypeptide encoding V_H/C_H having an anchor peptide of present claims 1-4, 6, 16, 18, 25, and 30; please refer to Figures 3-4, 6-7, 14-19 and columns 19-21, 24, and 28). Griffiths *et al.* also teach the Cre recombinase which cleaves the loxP site of the intervening sequence and is expressed in a separate plasmid (e.g. enzymatic proteolytic agent of present claims 11, 13, and 30; please refer to column 52, lines 45-55 and column 53, lines 19-24). In addition, Griffiths *et al.* teach that the replicable genetic display package can be a M13 bacteriophage or *E. coli* infected with an M13 bacteriophage (e.g. present claims 19-21, 25-26, and 35; please refer to column 7, lines 52-60, column 22, lines 59-67, and column 24, lines 3-35). Furthermore, Griffiths *et al.* teaches that a secretory leader peptide such as OmpA can be utilized to display the polypeptides (e.g. present claim 17; please refer to column 22, lines 65-66).

However, Griffiths *et al.* do not teach the use of urokinase as a proteolytic agent.

Goers et al. *et al.* teach attachment of a therapeutic agent to antibodies via a linker which may be cleavable by urokinase (e.g. please refer to column 3, lines 14-31). Goers *et al.* further teach that the linker can be an amine, a branched linker, proteolytic peptide linkers cleavable by urokinase, or a linker may have a spacer and a cleavable portion of a random construction (e.g. present claim 11, 29-31; please refer to columns 21-22, Tables III-V and VII-VIII, Example: Series IV-V). Therefore, Goers *et al.* specifically teaches a urokinase cleavable linker.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the display vectors of Griffiths *et al.* to incorporate a urokinase cleavable linker of Goers *et al.*

One having ordinary skill in the art would have been motivated to do this because Goers *et al.* teaches that although antibody carrier systems can be highly specific for the target site, a significant problem exists in that the therapeutic agent may not be released at the site and the linkage of the therapeutic agent to the antibody may interfere with antigen binding potentially reducing the effectiveness of the system, therefore, the use of a cleavage site to release the therapeutic agent from the antibody would be beneficial (please refer to column 4, lines 7-27). Furthermore, Griffiths *et al.* teach that the displayed antibodies can be removed from the genetically replicable package via proteolytic cleavage of the protein (please refer to column 27, lines 59-67). Therefore, one having ordinary skill in the art would be motivated to utilize the urokinase specific cleavage sequences taught by Goers *et al.* to remove the antibodies from the genetically replicable package taught by Griffiths *et al.*

There is a reasonable expectation of success in the modification of the antibody display system of Griffiths *et al.* with the urokinase cleavable linker of Goers *et al.* because of the examples taught by Goers *et al.* show the success of using urokinase cleavable linkers with an antibody conjugated to cells (please refer to Examples 9.1-9.4 and 10.2-10.4 of Goers *et al.*).

Therefore, the modification of the antibody display system taught by Griffiths *et al.* with the teachings of urokinase cleavable linkers by Goes *et al.* render the instant claims prima facie obvious.

Arguments and Response

17. Applicants' argument directed to the rejection under 35 USC 103(a) as being unpatentable over Griffiths *et al.* U.S. Patent No. 5,962,255 issued October 5, 1999 and Goers *et al.* U.S. Patent No. 4,867,973 issued September 19, 1989 for claims 1-4, 6, 11, 13, 16-21, 25-26, 29-31, and 35 was considered but was not found persuasive for the following reasons.

Applicants allege that Griffiths et al. does not teach a second polypeptide segment with a cleavable site and Goers et al. is utilized only for teaching the urokinase peptide cleavage sequence.

Applicants' arguments are not convincing since the combined teachings of Griffiths et al. and Goers et al. render the expression vector of the instant claims *prima facie* obvious. It is the Examiner's position that Griffiths et al. teach the first polypeptide as V_L and C_L, the second polypeptide as the selectable "marker peptide" and a loxP site, and the third polypeptide as V_H and C_H or V_H and C_{H1} with a g3 anchoring peptide (e.g. pIII, gIII, or coat protein III; present claims 18 and 25) (please refer to Figures 3-4, 6-7, 14-19 and columns 19-21, 24, and 28). Griffiths *et al.* also teach the Cre recombinase which cleaves the loxP site of the intervening sequence (e.g. second sequence) and is expressed in a separate plasmid (please refer to column 52, lines 45-55 and column 53, lines 19-24). Furthermore, Goers et al. is in fact utilized as evidence for a urokinase peptide cleavage sequence that can be attached to antibodies in order to ensure proper antigen binding (please refer to columns 3-4 and 21-22). Therefore, the teachings of Griffiths et al. and Goers et al. render the instant claims *prima facie* obvious.

Claim Rejections - 35 USC § 103

18. Claims 1-4, 6, 11, 13, 16-21, 25-26, 29-31, and 35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wang *et al.* U.S. Paten No. 6,833,441 B2 filed August 1, 2001 and Goers *et al.* U.S. Patent No. 4,867,973 issued September 19, 1989.

Wang *et al.* teach recombinant polynucleotides, vectors, and host cells for producing antigen-binding units (e.g. present claim 35; please refer to the "Abstract"). Wang *et al.* teach a light chain variable region fused to a heterodimerization sequence (e.g. first polypeptide), a "flexon" (e.g. second polypeptide), a heavy chain variable region fused to a second hetrodimerization sequence (e.g. third polypeptide) in a phage display vector and a host cell (e.g. present claims 1-3; please refer to column 4, lines 21-30, column 5, lines 48-61, column 6, lines 45-63,column 20, lines 1-15, column 26, lines 54-64, and column 38, lines 1-39). Additionally, Wang *et al.* also teach V_L, V_H, C_L, C_H, and C_{H1} (e.g. present claims 4 and 6; please refer to column 12, lines 3-10). In addition, Wang *et al.* teach the phage display vector as the filamentous phage M13 and fusion of antibody peptides to a phage coat protein specifically pIII of M13 (e.g. present claims 18-21 and 25-26; please refer to column 13, lines 47-52 and column 29, lines 49-65). Furthermore, Wang *et al.* also teach the use of OmpA for display in bacterial host cells including *E. coli* (e.g. present claim 17 and 25; please refer to column 30, lines 39-49 and column 35, lines 16-22). Moreover, Wang *et al.* teach protease cleavage sites between the heterodimerization sequences and phage coat protein (e.g. present claims 11, 13, 16, and 30-31; please refer to column 37, lines 1-7).

However, Wang *et al.* does not teach urokinase as a proteolytic agent.

Goers et al. *et al.* teach attachment of a therapeutic agent to antibodies via a linker which may be cleavable by urokinase (e.g. please refer to column 3, lines 14-31). Goers *et al.* further teach that the linker can be an amine, a branched linker, proteolytic peptide linkers cleavable by urokinase, or a linker may have a spacer and a cleavable portion of a random construction (e.g. present claim 29-31; please refer to columns 21-22, Tables III-V and VII-VIII, Example: Series IV-V). Therefore, Goers *et al.* specifically teaches a urokinase cleavable linker.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the antibody phage display vector of Wang *et al.* with the urokinase peptide cleavage sequence of Goers *et al.*

One having ordinary skill in the art would have been motivated to do this because Wang *et al.* teach about the instability of single chain antigen binding proteins and the potential interference of peptide linker sequences with antigen binding (please refer to column 2, lines 7-55 of Wang *et al.*). Furthermore, Goers *et al.* teaches that the linkage of the therapeutic agent to the antibody may interfere with antigen binding and potentially reduce the effectiveness of the therapeutic system, therefore, the use of a cleavage site to release the therapeutic agent from the antibody would be beneficial (please refer to column 4, lines 7-27 of Goers *et al.*). Therefore, a urokinase cleavable peptide linker taught by Goers *et al.* could be utilized to increase antigen binding by the proteins taught by Wang *et al.*

There is a reasonable expectation of success in the modification of the antibody phage display vector taught by Wang *et al.* with the urokinase cleavage sequence of Goers *et al.* because of the examples in Goers *et al.* showing the success of urokinase cleaving linkers joining

antibodies to therapeutic agents or cells (please refer to sections 9.1-9.4 and 10.2-10.4 in Goers *et al.*).

Therefore, the modification of the antibopdy phage display vector of Wang *et al.* with the urokinase cleavable sequence by Goers *et al.* would render the instant claims prima facie obvious.

Arguments and Response

19. Applicants' argument directed to the rejection under 35 USC 103(a) as being unpatentable over Wang *et al.* U.S. Paten No. 6,833,441 B2 filed August 1, 2001 and Goers *et al.* U.S. Patent No. 4,867,973 issued September 19, 1989 for claims 1-4, 6, 11, 13, 16-21, 25-26, 29-31, and 35 was considered but was not found persuasive for the following reasons.

Applicants allege that Wang et al. does not teach a second polypeptide sequence that can be cleaved and that Goers et al. is cited merely for the teaching of a urokinase peptide cleavage sequence.

Applicants' arguments are not convincing since the combined teachings of Wang et al. and Goers et al. render the expression vector of the instant claims *prima facie* obvious. It is the Examiner's position that Wang et al. teach a light chain variable region fused to a heterodimerization sequence (e.g. first polypeptide), a "flexon" (e.g. second polypeptide), a heavy chain variable region fused to a second hetrodimerization sequence (e.g. third polypeptide) in a phage display vector and a host cell (e.g. please refer to column 4, lines 21-30, column 5, lines 48-61, column 6, lines 45-63,column 20, lines 1-15, column 26, lines 54-64, and column 38, lines 1-39). In addition, Wang *et al.* teach protease cleavage sites (e.g. second polypeptide) between the heterodimerization sequences (e.g. first polypeptide) and phage coat protein (e.g.

third polypeptide; please refer to column 37, lines 1-7). In addition, Goers et al. is in fact utilized as evidence for a urokinase peptide cleavage sequence that can be attached to antibodies in order to ensure proper antigen binding (please refer to columns 3-4 and 21-22). Therefore, the teachings of Griffiths et al. and Goers et al. render the instant claims *prima facie* obvious.

Future Communications

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amber D. Steele whose telephone number is 571-272-5538. The examiner can normally be reached Monday through Friday 9:00AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on 571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

ADS
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